孤独症谱系障碍多模态磁共振脑影像模式识别¯

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摘要 孤独症谱系障碍(Autism spectrum disorder, ASD)是一组高度复杂的神经发育障碍。ASD患病率日趋升高、异质性强、会造成终生影响，但其神经病理机制仍不清楚。磁共振多模态脑影像为揭示 ASD 的影像学脑机制提供了新的手段。基于单模态磁共振脑影像的研究已经发现了 ASD 在大脑结构、功能及脑网络层面都表现出了广泛的异常，其异常区域包括了杏仁核、梭状回、眶额皮层、内侧前额叶、前扣带、颞顶联合区以及脑岛等，这些脑区大多都涉及到了“社会脑”网络。虽然图像级融合、特征级融合、决策级融合的多模态脑影像分析框架在揭示被试神经机制过程中提供了多维度、多层级的信息，但是基于多模态磁共振脑影像融合的 ASD 研究还处于起步阶段。基于磁共振脑影像的 ASD 辅助诊断及亚型划分有望为临床诊疗提供客观依据。未来的研究可以构建一个融合多模态脑影像的分析框架，结合大脑功能、结构以及网络等多维度信息，全面刻画 ASD 发生发展规律，揭示其非典型神经发育机制。除此之外，未来的研究需要深入挖掘 ASD “社会脑”网络异常机制，探索 ASD 社交障碍环路，寻找潜在精准神经调控靶点，助力临床实现 ASD 精准诊疗。

关键词 孤独症谱系障碍，多模态磁共振，大脑功能和结构，辅助诊断，亚型分类

1 引言

孤独症谱系障碍(Autism spectrum disorder, ASD)是一组患病率日趋升高、高异质性且严重影响儿童健康的神经发育障碍。ASD 的核心症状表现为社交沟通障碍、兴趣狭窄以及重复刻板行为，同时可能伴有感知觉异常等症状(Lai et al., 2014)。美国疾控中心最新发布数据显示，ASD 的发病率约为 1/36 (Maenner et al., 2023)。我国虽缺少全国性的 ASD 发病率调查数据，但 2022 年发布的《中国孤独症教育康复发展状况报告 IV》显示我国的 ASD 发病率约为 1% (王培实, 2022)。由此推算，在我国，ASD 人群已超 1000 万。ASD 已经成为日趋严重的全球公共卫生健康问题。

现阶段，ASD 的发病机制还不清楚。现有研究表明 ASD 是多种因素共同作用的结果，包括了遗传因素、神经发育问题、环境因素、免疫系统异常、神经递质失衡等(Keil & Lein,

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2016; Livingston & Happé, 2017; Quesnel-Vallieres et al., 2019; Won et al., 2013)。随着神经科学和人工智能技术的不断进步，磁共振脑影像为揭示 ASD 的神经影像机制提供了新的视角，有望为实现 ASD 精准诊疗提供客观依据(Duan & Chen, 2022)。过去十多年，研究人员利用结构磁共振成像(structural magnetic resonance imaging, sMRI)、功能磁共振成像(functional magnetic resonance imaging, fMRI)、弥散张量成像(diffusion tensor mapping, DTI)、磁共振波谱成像(magnetic resonance spectrum, MRS)等手段, 从多个角度揭示了 ASD 大脑灰质、白质、大脑激活、功能连接、大尺度脑功能网络等指标的异常(Duan et al., 2020; Guo et al., 2019; Guo, Duan, Suckling, et al., 2020; He et al., 2018; He et al., 2021; Yeh et al., 2022; Y. Zhao et al., 2022)。基于以往的发现，研究人员提出了杏仁核理论、社交动机理论、镜像神经元系统理论等假说来解释 ASD 的异常(Baron-Cohen et al., 2000; Chevallier et al., 2012; Hamilton, 2008)。另外，随着信息融合技术的不断进步，研究人员尝试将多模态磁共振脑影像融合起来，多层级、全方位、多角度对疾病进行表征，以此来达到用于临床诊断和治疗评估的目的(He et al., 2020; Hirjak et al., 2022; Maglanoc et al., 2020; Park et al., 2021; Weng et al., 2020; Zhang et al., 2020)。例如，Park 等人融合功能连接及结构连接，基于黎曼优化算法探究了 ASD 结构与功能耦合的关系，发现 ASD 结构功能耦合差异反映了 ASD 症状的个体差异(Park et al., 2023)。Kim 等人基于 T1 加权成像和 DTI 的特征建立了 ASD 辅助诊断模型，分类准确率达到了 88.8%。

无论是基于单模态的研究，还是多模态融合的研究都加深了我们对 ASD 大脑影像学神经机制的理解，但是他们都有各自的优势和不足。单模态脑影像研究虽然分析手段简单明了、聚焦于特定的研究问题，但是无法捕捉到模态之间的互补的信息，无法多层级、全方位探索 ASD 大脑的功能与结构的异常机制。多模态脑影像融合虽然整合了多维度信息，但是也面临着融合难、可解释性差等问题，而且多模态脑影像融合的分析框架在 ASD 研究中的应用并不广泛。因此，本文评述了现阶段 ASD 单模态脑影像研究的发现，从图像级融合、特征级融合及决策级融合三个层面梳理了多模态脑影像融合方法及在 ASD 研究中的初步应用，总结了现有 ASD 磁共振脑影像研究的优势和不足，并在文章最后提出了对未来研究的思考和展望，为后续 ASD 脑影像及其他精神疾病或神经发育障碍的研究提供重要支撑。

2 ASD 单模态脑影像研究

磁共振成像技术因其无辐射、无侵入性、高分辨率等优势，在 ASD 研究中得到了广泛的应用。以往的研究不但探究了结构和功能影像在局部特征的异常，而且从网络水平探究了结构网络或者功能网络的异常。通常，这些异常与 ASD 的临床特征表现出了一定的关联性，

这对理解 ASD 的起因、神经机制以及促进早期诊断和指导康复治疗都具有重要意义。

2.1 ASD 脑影像局部异常研究

2.1.1 ASD 结构影像局部特征异常研究

结构影像学研究通常采用 T1 加权成像和 DTI, 其中 T1 加权成像常被用来测量大脑的灰质体积以及皮层厚度等形态学指标，而 DTI 常被用来评估大脑白质纤维束的微观结构以及传导通路。

基于 T1 加权成像的研究报告了 ASD 儿童相较于典型发育(typically developing, TD)在右侧角回、左侧额中回、左侧额上回、左侧楔前叶、左侧枕下回、右侧颞下回表现出了增加的灰质体积；在左侧小脑以及左侧中央后回表现出了降低的灰质体积；而且发现右侧角回增加的灰体积与 ASD 的重复刻板行为显著相关(Liu et al., 2017)。也有研究表明，ASD 成年人相较于 TD 在右侧枕下回、左侧梭状回、右侧颞中回、双侧杏仁核、右侧额下回、右侧眶额皮层以及左腹内侧前额叶都表现出了降低的灰质体积(Sato et al., 2017)。同时，Yang 等人发现 ASD 成年人相较于 TD 在左侧颞中回、左侧颞上回、左侧海马旁回以及右侧中央后回表现出显著升高的灰质体积，而在右侧小脑、左侧前扣带显著降低的灰质体积 (Yang et al., 2016)。梳理这些异常区域可以发现，灰质体积的异常区域与默认网络(default model network，DMN)有很大的重叠。DMN 被认为是参与内省和自我反思的主要网络之一，在记忆以及情感调节等过程中都扮演着重要的角色(Raichle et al., 2001; Sheline et al., 2009)。ASD 在 DMN 区域的异常可能导致其在自我认知等方面存在问题，进而影响他们对社交互动的参与和感知(Padmanabhan et al., 2017; Washington et al., 2014)。除此之外，基于 T1 加权成像的研究还报告了 ASD 儿童及青少年在大脑左半球表现出大范围显著增加的皮层厚度，而 ASD 成年人在额叶表现出了降低的皮层厚度 (Khundrakpam et al., 2017; Premika S.W. Boedhoe et al., 2020)。

研究所使用的被试数量以及 ASD 的异质性可能会导致部分研究结果不一致。同时，ASD 是一组神经发育障碍，年龄是主导研究结果的主要因素。回顾以往的研究发现，ASD 在不同年龄段都表现出了大脑灰质体积和皮层厚度偏离 TD 发育轨迹的模式(Khundrakpam et al., 2017; Koolschijn & Geurts, 2016; van Rooij et al., 2018; Wang et al., 2017; Yamasaki et al., 2010; Zabihi et al., 2019; X. Zhao et al., 2022)。研究人员由此推测，ASD 在早期表现出了过度发育，而在儿童后期表现出了生长减缓甚至停滞发育，在此之后表现出了大脑灰质体积和皮层厚度加速衰减现象(Lange et al., 2015; Zielinski et al., 2014)。因此，后续的研究需要建立一个发育的框架去探究 ASD 形态学的异常。

各向异性分数(fractional anisotropy, FA)常常在DTI研究中被用来刻画大脑白质纤维的完

整性。FA 值降低反映了大脑白质纤维束组织结构完整性受损。对于 ASD 儿童以及成人，大部分研究都发现 ASD 相较于 TD 表现出了降低的 FA，其中降低的区域包括了腹内侧前额叶皮层、眶额、前扣带回、颞顶联合区、双侧颞上沟、颞枕束、胼胝体、(Alexander et al., 2007; Barnea-Goraly et al., 2004; Haigh et al., 2020; Lee et al., 2007; Pardini et al., 2009; Sundaram et al., 2008; Temur et al., 2019)。但是也有研究发现，ASD 儿童在左侧内囊后肢、胼胝体膝部、胼胝体压部、左侧外囊表现出了升高的 FA；ASD 青少年在额叶、右侧扣带回、双侧脑岛、右侧颞上回、双侧小脑中脚表现出了升高的 FA(Bashat et al., 2007)。除了 FA，平均弥散程度(mean diffusivity, MD)也被用来探究大脑白质的微观结构。MD 反映了平均弥散水平和弥散阻力的整体情况。相较于 TD，ASD 在胼胝体、扣带等区域都表现出了 MD 的升高(Cai et al., 2022; Valenti et al., 2020)。ASD 被试 FA 及 MD 的异常表明白质结构异常在其病理机制中可能扮演着重要的作用。近些年，一些研究人员除了探究白质的结构外，还开始探究白质的功能，然而 ASD 大脑白质功能的异常还不清楚，未来的研究还需要探究 ASD 白质功能异常以及白质功能异常与行为之间的关系(Li et al., 2019; Peer et al., 2017)。

2.1.2 ASD 功能影像局部特征异常研究

fMRI 通过检测大脑血氧饱和度的变化来反映各个部位神经元群的活动水平，是探测人类大脑功能活动的重要手段。在神经影像研究中，功能影像学研究主要包括了任务态研究以及静息态研究两大方向。

ASD 任务态 fMRI 研究主要探究了其面孔加工、运动感知、语言加工以及奖赏处理等方面的异常(Hernandez et al., 2015)。在面孔加工过程中，大部分研究发现 ASD 梭状回和杏仁核的激活降低(Corbett et al., 2009; Kleinhans et al., 2011; Nickl-Jockschat et al., 2015; Nomi & Uddin, 2015)，且梭状回的激活水平与社交焦虑存在显著的负相关(Kleinhans et al., 2010)。然而，有研究发现 ASD 在处理其母亲面孔过程中梭状回的激活与 TD 的激活水平相当，然而在处理陌生人面孔过程中表现出了激活降低(Pierce & Redcay, 2008)。上述结果表明，ASD 对陌生面孔照片处理过程中的所产生的焦虑可能导致了其社交回避情况的出现。在运动感知过程中，ASD 在颞上沟、腹外侧前额叶、颞顶联合区都表现出了降低的激活(Davies et al., 2011; Koldewyn et al., 2011; von dem Hagen et al., 2013)。迅速感知生物运动可以引导注意力集中于出现的社交刺激，而 ASD 对于生物运动感知的异常可能导致在社交场景中不能很好捕获社交线索。在语言处理过程中，相较于 TD，ASD 的 Broca 区域、颞叶前部表现出激活更强(Graves et al., 2022; Knaus et al., 2008)，而在左腹侧中央沟、颞上沟的激活降低(Tanigawa et al., 2018)。同时，有研究发现，ASD 在语言处理过程中左右半球功能分化程度降低(Deemyad, 2022;

Knaus et al., 2010)。在奖赏信息处理过程中，在金钱奖赏或者社会奖赏条件下，ASD 的伏隔核、杏仁核、前扣带、腹侧纹状体等区域都表现出了激活降低(Baumeister et al., 2023; Kohls et al., 2018; Kohls et al., 2013)。因此，大脑奖赏环路的异常可能导致 ASD 对于社会性刺激的敏感程度降低，并且导致其兴趣狭窄等症状。

ASD 静息态 fMRI 研究主要包括了静态功能连接研究与动态功能连接研究两大方向。过去二十年，大量研究发现了 ASD 静态功能连接的异常。但是，有研究发现 ASD 表现出超连接，有研究发现 ASD 表现出失连接，也有研究发现 ASD 超连接和失连接两者都存在(Di Martino et al., 2011; Hull et al., 2016; Oldehinkel et al., 2019; Reiter et al., 2019; Uddin et al., 2013; Xiao et al., 2023)。为了解释这一现象，Uddin 等人梳理以往研究文献后从发发育角度提出了“超连接-失连接”模型，该模型表明 ASD 在青少年以及成年时期通常表现为失连接，而在儿童时期表现为超连接(Uddin et al., 2013)。但是，ASD 静态功能连接从超连接转变为失连接过程的具体时间节点还不清楚。另外，越来越多的研究表明，人类大脑的功能连接模式会随时间而变化(Chang & Glover, 2010)。利用动态功能连接分析方法可以捕捉大脑功能连接的时变特性，这将有助于理解大脑功能组织架构和信息加工基础，并且有可能调和以往静态功能连接研究发现不一致的情况(Gonzalez-Castillo & Bandettini, 2018; Preti et al., 2017; Shine & Poldrack, 2018)。有研究使用滑动窗分析方法，发现 ASD 在后扣带和颞极中部、额下回的动态功能连接变异性升高，而后扣带与中央前回之间动态功能连接变异性降低，并且后扣带动态功能连接的异常与 ASD 社交症状严重程度显著相关(He et al., 2018; Y. Li et al., 2020)。也有研究发现，无论在半球内还是半球间，相较于 TD，ASD 的前扣带、内侧前额叶都表现出了升高的动态功能连接密度变异性，而在梭状回、颞下回表现出了降低的动态功能连接密度变异性。同时，ASD 的感觉运动区在半球内表现出降低的动态功能连接密度变异性(Guo, Duan, Chen, et al., 2020)。动态功能连接分析为 ASD 脑功能探究提供了新的视角，然而将来还需要结合动态、静态进行分析，探明 ASD 大脑功能活动异常与其症状、基因表达之间的关系。

2.2 ASD 脑网络研究

人类大脑是一个复杂的网络。研究人员通常从结构和功能两个角度来构建大脑网络。脑网络分析提供了从系统水平对大脑的功能组织、信息交互甚至疾病的病理机制进行研究的手段(Bullmore & Sporns, 2009)。大量研究表明，ASD 的脑功能网络与结构网络都存在异常(Duan et al., 2020; He et al., 2018; He et al., 2021; Rudie et al., 2013; Yang et al., 2023)。

大脑的功能网络通常基于功能连接来构建。基于图论分析的研究发现：在全局水平，

ASD 功能网络的聚类系数和最短路径长度显著降低，这表明 ASD 的功能网络更偏向于随机化;在局部水平，ASD 的双侧颞上沟、右背外侧前额叶以及楔前叶等区域丧失了中心节点的属性 (Itahashi et al., 2014)。同时，也有研究发现，ASD 在双侧颞边缘区域的度中心性增加(Di Martino et al., 2013)。另外，Menon 提出了的三网络模型来帮助理解精神和神经疾病的认知和情感障碍失调(Menon, 2011)。该模型认为，DMN、突显网络(salience network , SN)、额顶网络(frontoparietal network, FPN)功能及其动态交互异常是包括 ASD 在内的精神疾病及神经发育障碍的起因之一。已经有研究报道了 ASD 三网络之间的静态、动态的交互异常，并且这些异常与ASD的核心症状显著相关(Guo et al., 2023; Hogeveen et al., 2018; Qing Wang et al., 2021)。大尺度功能网络的分析为表征精神疾病或者神经发育障碍提供了新的手段。但是，未来的研究还需要分析大尺度功能网络的交互异常与结构网络异常之间的潜在关系。

结构网络对大脑的功能活动起着一定的约束作用。结构连接的异常可能导致认知、情感功能失调，进而在临床上表现出某种疾病的症状。大脑的结构网络通常基于白质纤维连接来构建。研究发现，对于 FA 值构成的结构网络，ASD 的小世界属性降低，全局的效率升高，并且额下回、中央后回、左侧楔前叶、丘脑、双侧顶上皮质的节点效率增加(Cai et al., 2022; Qin et al., 2018)。现阶段，也有研究利用灰质体积或者皮层厚度构建结构协变网络来探究脑区间形态学的协同变化与大脑发育、认知以及疾病病理机制之间的关系(DuPre & Spreng, 2017; Montembeault et al., 2016; Prasad et al., 2022; Sha et al., 2022; Zielinski et al., 2010)。相较于 TD，研究发现 ASD 的半球间皮下区域的协变降低，而半球内皮下区域的协变增强(Duan et al., 2020)，并且 ASD 的结构协变网络在内侧额叶、顶叶以及颞-枕皮层的节点中心性降低(Balardin et al., 2015)。结构网络研究从网络水平定量刻画 ASD 的大脑结构，有助于理解大脑信息传递及加工机制，了解 ASD 大脑的发生发展规律，可能为理解 ASD 的病理机制提供关键线索。

3 ASD 多模态脑影像融合

ASD 等神经发育障碍和精神疾病影像学研究的一个重要目的是对其进行全面表征，揭示其神经病理机制。少量的大脑疾病可以利用单模态影像就能实现精确刻画，但是对于大多数早期非器质性病变的精神疾病，单模态脑影像提供的信息具有一定局限性，还需要融合多模态脑影像进行多层级、全方位、多角度表征，以此来达到用于指导临床诊断和治疗评估的目的(Calhoun & Sui, 2016)。虽然研究人员早已提出了多模态脑影像融合研究的构想，但是如何真正做到多模态脑影像融合是该领域一直面临的挑战。因此，本小节从图像级融合、特

征级融合、决策级融合三个层级梳理了多模态脑影像方法及其在 ASD 研究中的应用。

3.1 图像级融合

图像级融合是多模态脑影像融合最底层、最简便的融合方式。例如，T1 加权成像常用于大脑解剖成像，其很好地反映了大脑的灰质和白质；T2 加权成像常用于观察大脑病变，对出血较为敏感，伪影相对较少；而 T1/T2 的比率图则可以用来反映人类大脑皮层中髓鞘化的程度。这种基于 T1 和 T2 成像融合所得到的髓鞘化图谱已被证明与人类皮层进化扩张、非人灵长类动物的神经元密度图谱等具有显著的相关性(Glasser & Van Essen, 2011)。分子遗传学研究也已经发现了在 ASD 中髓鞘化相关的基因表达异常(Richetto et al., 2017; Zhao et al., 2018)。T1 和 T2 图像级的融合研究为这一发现提供了影像学证据。Daeki 等人发现 ASD 高风险婴儿大脑灰质和白质都表现出了广泛的 T1/T2 的值降低，而且 T1/T2 的值与行为发育水平表现出了显著的正相关(Darki et al., 2021)。这些发现表明，T1/T2 的值是一个对于发育较为敏感的指标，后续的研究还需要利用该指标探索髓鞘化异常在 ASD 病理机制中扮演的角色。

除了 T1/T2 这种融合方式，研究人员还提出了联合独立成份分析(joint-independent component analysis, j-ICA)、多模态典型相关分析(multimodal canonical correlation analysis, mCCA)、偏最小二乘等多变量方法，通过寻找被试多种模态数据之间相互独立且共变或被试间共变最大或不同模态之间最为相关的成份(或模式)来实现影像数据级的融合(Qi et al., 2018; Qi et al., 2019; Sui, Adali, et al., 2012; Sui, Yu, et al., 2012)。Qi 等人利用 mCCA+jICA 融合大脑灰质与功能活动，发现了 ASD 不同亚型之间共有的结构与功能协同变化的脑区以及亚型间特异性变化的脑区(Qi et al., 2020)。基于 mCCA+jICA 方法，研究人员融合了任务态数据与大脑灰质数据，发现了与新颖性追求特征相关的脑区，实现了对酗酒、吸烟、注意缺陷/多动障碍、抑郁、精分等风险因子的预测与分类(Qi et al., 2021)。然而，这种数据驱动的多模态影像融合分析方法在 ASD 中的应用并不广泛，未来的研究还需要挖掘 ASD 不同模态脑影像之间的协同变化关系，探究具有 ASD 特异性的影像学标记物。

3.2 特征级融合

特征级融合是多模态脑影像融合最常见的融合方式。不同模态的影像提供了各种各样的特征，例如，可以从 T1 加权影像获得灰质体积、灰质密度、皮层厚度、灰白质对比度、沟回指数等特征；可以从功能影像获得功能连接、功能连接密度、低频振荡幅度、局部一致性、动态功能连接、动态功能连接变异性等指标；可以从弥散张量影像获得 FA、MD、径向扩散系数、轴向扩散系数、纤维束条数、纤维束密度等指标。基于上述指标，特征级的融合大

致可以分为特征耦合模型、特征联合筛选模型、相似性网络模型以及大尺度神经环路模型四种方式。

特征耦合模型研究中最常见的是结构与功能之间的耦合。一般情况下，耦合性定义为两种指标的相关系数(Baum et al., 2020; Zhang et al., 2011)。以往的研究表明，耦合性这种综合了结构指标与功能指标的测量方式要比任何单一模态探测脑疾病的生理异常更为敏感。例如，Zhang 等人将结构连接与功能连接的皮尔逊相关系数定义为结构与功能的耦合性，研究结果发现，在全面性癫痫患者中，结构与功能连接的耦合性显著降低，且与病程呈现出负相关(Zhang et al., 2011)。在 ASD 研究中，Ma 等人发现 ASD 的左上放射冠和内囊左后肢白质体积与局部一致性的耦合程度降低(Ma et al., 2022)。最近，也有研究发现，在 TD 中，外侧前额叶的结构与功能的耦合性与执行功能显著相关并且部分介导年龄与执行功能的关系(Baum et al., 2020)。研究人员还提出用预测模型来刻画结构与功能耦合的关系，结果表明结构与功能从单模态区域到跨模态区域表现出了一种梯度变化的解耦合模式(Vázquez-Rodríguez et al., 2019)。何等人利用这种预测模型发现，ASD 的右侧辅助运动区、右侧脑岛和左侧额下回的结构和功能耦合异常高于 TD，并且异常区域的结构功能耦合值可以用来预测 ASD 的临床症状(何长春, 2021)。以往这些研究表明，结构和功能之间的耦合关系可能为理解 ASD 的病理机制和临床诊疗提供新思路。然而，目前对于 ASD 的结构和功能耦合关系的研究还较少，在后续的研究中还需要继续探索。

特征联合筛选模型通常被用来融合多模态影像特征对被试进行分类或者预测其临床症状。通常，融合多种模态的特征将获得更高的分类准确率或者更好的预测效果(Liem et al., 2017; Meng et al., 2017; Qi Wang et al., 2021)。例如，He 等人利用交叉验证递归特征消除法筛选了结构网络特征和功能网络连接特征后，基于支持向量回归预测了脑年龄，发现 ASD 在儿童期脑年龄显著高于其实际年龄，而在青少年期脑年龄显著低于其实际年龄，这表明 ASD 在儿童期大脑表现出了加速发育，而在青春后期大脑发育开始变得迟缓(He et al., 2020)。

相似性网络模型是融合多模态影像揭示大脑皮层宏观组织结构的一种新手段(Seidlitz et al., 2018; Yang et al., 2021)。通常利用单个被试内区域间多个不同模态指标的相关性来构建相似性网络，其中包括了形态学相似性和功能相似性网络(J. Li et al., 2021; Meng et al., 2022)。相似性网络分析在抑郁症、精神分列症等疾病中已经得到了广泛应用(J. Li et al., 2021; Martins et al., 2022; Xue et al., 2023; Zong et al., 2023)。例如，Li 等人融合皮层表面积、灰质体积、皮层的厚度、高斯曲率、平均曲率、FA 以及平均弥散程度等指标构建了形态学相似性网络，发现了抑郁症患者形态学相似性网络的异常，并找出了与形态学相似性网络异常相

关的基因，发现这些基因主要富集在小胶质细胞和神经元细胞(J. Li et al., 2021)。相似性网络模型提供了一种新颖的、稳定的以及具有神经可解释性的手段去理解人类大脑的网络结构。然而，ASD 形态学及功能相似性网络的异常及其潜在的分子机制还不清楚。未来的研究需要从结构及功能两个角度出发，分别构建相似性网络，探究 ASD 相似性网络的异常与基因表达、细胞层流分化等微观指标的关系。

大尺度神经环路模型是一个强有力的建立大脑微观环路和宏观组织关联关系的方法(Breakspear, 2017; Kong et al., 2021; P. Wang et al., 2019)。简单来说，该模型基于脉冲神经网络模型和血氧动力学模型，融合结构连接和功能连接，模拟出了大脑微观神经环路的动力学特性，包括了大脑区域内循环(或周期)输入、外部输入以及神经噪声等。研究人员已经基于大尺度神经环路模型开展了多项研究，例如，Weng 等人发现了颞叶癫痫患者和全面性癫痫患者的循环输入和外部刺激输入的异常，且发现不同的癫痫亚型是由不同的微观环路特征紊乱导致的(Weng et al., 2020)；Park 等人发现 ASD 的循环输入和外部输入的改变与结构连接流行的畸变相关(Park et al., 2021)；Kong 等人发现感觉运动皮层是大脑功能连接动态性的驱动器。经颅磁刺激、经颅直流电刺激等手段已经在神经调控领域发挥了重要作用，但是现阶段还缺乏可靠、稳定、高效的个性化干预靶点(Cash et al., 2021; Cocchi & Zalesky, 2018)。构建精确的大尺度神经环路模型为我们提供了一个数字孪生脑，如果通过数字孪生脑仿真计算出 ASD 神经个体化精准调控的靶点，将可能获得更加显著的治疗效果。

3.3 决策级融合

决策级融合是指根据一定的规则对不同模态影像的特征进行提取后构建分类器，再将多个分类器的判别结果进行融合后作出全局最优的决策(黄渝萍, 李伟生, 2023)。Dimitriadis 等人基于决策融合的思想，利用多种形态学指标，通过集成学习算法，实现了对健康对照、早期轻度认知障碍、晚期轻度认知障碍、阿尔兹海默症的多分类(Dimitriadis et al., 2018)。在 ASD 中也有类似的研究出现。例如，有研究训练了基于结构连接和功能连接的集成分类器，在单中心内实现了对 ASD 的精确分类；而 ElNakieb 等人融合三通道的初级分类器进行综合决策，最后对 ASD 的分类准确率达到了 80.5% (Dekhil et al., 2019; ElNakieb et al., 2018)。现阶段基于决策级融合的研究大多集中于结构和功能影像，未来的研究可以考虑纳入磁共振波谱特征、电生理特征以及生化特征来综合多角度信息进行综合决策。

4 ASD 辅助诊断

ASD 患病率日趋升高、异质性强、诊断难、负担重(Lai et al., 2014; Maenner et al., 2023)，

早发现、早诊断、早干预可以明显改善预后。如何实现 ASD 精确诊断是当前研究的热点问题(Kaur & Kaur, 2023)。以往的大多数研究都采用单模态脑影像进行分类。Anderson 等人基于功能连接在小样本上对 ASD 和 TD 进行分类，准确率达到了 79% (Anderson et al., 2011)。基于小样本数据训练的模型，可能受到数据量及 ASD 异质性等影响，不具有鲁棒性(Robust)和推广性。因此，研究人员逐渐转向对多中心大样本的分析，以此来提升模型鲁棒性和泛化能力。例如，Nielsen 等人基于多中心公开数据库，在大样本上基于功能连接实现了超过 60%的分类准确率(Nielsen et al., 2013)。除了功能连接，一些结构指标也经常被用来用于 ASD 的分类(Ali et al., 2022; Uddin et al., 2011)。例如，Gori 等人基于灰质体积、皮层厚度、表面积等形态学指标实现了对 ASD 的分类(Gori et al., 2015)；ElNakieb 等人基于 DTI 数据的 FA、平均弥散程度等特征实现了对 ASD 的分类(ElNakieb et al., 2021)。

基于单模态的识别往往不能获得优异的分类准确率，距离临床应用还有很远的距离。因此，研究人员尝试基于更全面的多模态影像来提升分类准确率(Kim et al., 2022; Libero et al., 2015; Liu et al., 2015)。例如，有研究融合了结构和功能连接数据，采用自编码模型和多层感知机，对 ASD 的分类准确率达到了 85.06%(Rakić et al., 2020)；而 Kim 等人将 T1 影像和 DTI 影像的特征融合能获得了 88.8%的分类准确率 (Kim et al., 2022)。

除了应用类似于支持向量机、随机森林、多层感知机等传统的机器学习方法对 ASD 进行分类识别外，深度学习技术作为机器学习的一个重要分支，依靠其强大的学习能力也逐渐被广泛应用于辅助诊断的研究中。构建多模态脑影像之间的关联关系、建立参数共享的高效任务模型、在小样本下实现精准诊断分类以及如何解释深度学习的过程都是基于深度学习的多模态脑影像模式识别研究热点。现阶段，基于深度学习的 ASD 分类研究主要包括了基于深度神经网络和基于图神经网络两大类型(Cackowski et al., 2023; Guo et al., 2017; Khodatars et al., 2021; Li et al., 2018)。

深度神经网络是许多人工智能应用的基础，它利用多层无监督隐藏层将现有空间的样本逐层映射到另一个空间，对高度复杂的函数进行拟合，以此来实现对输入特征更好的表达。有大量的研究基于功能或者结构影像数据，利用深度神经网络及其衍生的模型对 ASD 进行分类(Eslami & Saeed, 2019; Ismail et al., 2017; Leming et al., 2020; C. Wang et al., 2019; Xiao et al., 2018)。例如，Kong 等人将功能连接作为输入，利用深度神经网络模型对 ASD 的分类准确率达到了 90.39%(Kong et al., 2019)；Pinaya 等人基于结构影像，利用深度自编码模型建立了标准模型，将 ASD 偏离标准范围的偏差作为特征，实现了对 ASD 的分类(Pinaya et al., 2019)；而 Mostafa 等人融合了结构和功能影像特征，基于自编码模型和深度神经网络对 ASD

的分类准确率达到了 79.2%(Mostafa et al., 2020)。在这里我们发现，融合了多模态信息的分类准确率在一些情况下并没有优于单模态影像特征，这可能与样本数量、选择的模型、选取的特征有一定的关系。如何在有限样本上，训练具有稳定性、可泛化性、高分类准确率的深度神经网络将是下一步需要着力解决的问题。

图神经网络是一种处理图形结构数据的人工神经网络，它可以对节点和边进行建模，并能够在学习过程中捕捉节点之间的相互作用和全局特征。大脑是一个复杂但又高效的系统，它由几百亿个神经元之间的几万亿条突触连接组成(Bullmore & Sporns, 2009)。传统的卷积神经网络没有考虑不同节点之间的相互作用，忽略了大脑功能和结构之间的“深度关系”，而图神经网络展现出了其自身对于复杂网络建模的优势。因此，对于脑影像研究来说，可以将大脑的节点抽象为图中的节点，而脑区之间的关系可以抽象为图中的边，进而利用图神经网络对非欧空间具有更强表达能力的优势来实现对被试特征的精准预测或分类(Bessadok et al., 2022; X. Li et al., 2021; X. Li et al., 2020; Yang et al., 2019)。现阶段，已有研究利用图神经网络尝试对 ASD 进行识别。例如，Chen 等人将感兴趣区域的灰质密度、慢 4 和慢 5 频段的低频振幅作为节点特征，将感兴趣区域间的功能连接作为边构建了多模态个体水平的图网络，基于图神经网络模型，在大样本数据集上对 ASD 的分类准确率达到了 74.7% (Chen et al., 2022)；而 Yin 等人将大脑不同脑区的基于图论的局部属性等(如，度中心性等)作为节点特征，功能连接做为边构建图，基于图神经网络对 ASD 的分类准确率达到了 82.3% (Yin et al., 2021)。对未来研究中的图神经网络模型而言，如何参考大脑的高效处理网络构建具有生理意义的图结构可能是获得优异性能的关键。图神经网络与大脑网络的结合，不但可以使得我们搭建的系统更加灵活，也可能帮助我们理解大脑的信息加工处理机制并找出 ASD 等神经发育障碍或精神疾病特异性的神经环路，为临床实现精准医疗提供科学依据。

无论是基于单模态脑影像，还是基于多模态脑影像融合技术；无论是利用传统的机器学习框架，还是利用最新的深度学习技术，建立高特异性、高灵敏性的 ASD 辅助诊断系统是研究人员一直追求的目标。以多模态脑影像为核心，建立符合中国国情、具有高稳定性、高推广性、可在 ASD 专业诊断人员匮乏地区进行推广的 ASD 辅助诊断平台是未来需要着力发展的方向。

5 ASD 亚型识别

ASD 不是单一的临床实体，是一组具有高度异质性的神经发育障碍(Masi et al., 2017)。异质性是理解 ASD 神经病理机制及实现精准诊疗的最大阻碍之一(Georgiades et al., 2013)。

亚型划分是 ASD 异质性研究中最常采用的手段。以往对于 ASD 的亚型划分大多基于行为学的表现。例如，美国精神障碍诊断与统计手册(The diagnostic and statistical manual of mental disorders, *DSM*)-*III* 和 *DSM-IV* 将 ASD 划分为阿斯伯格综合征、未分类的广泛性发育障碍以及典型孤独症(Kim, 2020)。过去十多年，临床上基于行为学的亚型划分将 ASD 划分为几个言语水平、认知能力、社交沟通水平、重复刻板水平等具有差异的亚组，这虽然有助于揭示 ASD 的症状发育轨迹的异质性(Kim et al., 2018)。但是，行为学的亚型对于揭示 ASD 的神经机制及指导临床实现精准诊疗的作用似乎有限。近年来，随着脑影像分析手段的不断进步，划分 ASD 影像学亚型对于理解其神经机制显示出了一定的优势。尽管使用的数据、分析手段都各不相同，但是现有的研究表明基于脑影像可以将 ASD 划分为 2~4 种亚型(Chen et al., 2019; Easson et al., 2019; Hong et al., 2018; Hong et al., 2020; Stefanik et al., 2018; Wang, 2022)。例如，Easson 等人基于功能连接将 ASD 划分为具有 2 种不同连接模式的亚型(Easson et al., 2019)；Chen 等人将 ASD 大脑灰质相较于 TD 的差异作为特征，发现了 3 种具有不同临床症状和功能连接模式的 ASD 亚型(Chen et al.,2019)；Hrdlicka 等人将额叶的皮层厚度，纹状体、海马、尾状核及杏仁核的大小等特征进行聚类，发现了 4 种具有不同感兴趣区域特征的 ASD 亚型(Hrdlicka et al., 2005)。总结以往的研究，发现有的 ASD 亚型在特定的脑影像特征上相较于 TD 表现出了增加，而有的亚型表现出减少的情况，这表明异质性在影像研究中是不可忽略的因素。另外，基于功能连接的亚型研究发现，DMN 和额顶网络的异常在不同的亚型中都是一致存在的，这表明这些高级认知网络的异常可能是导致 ASD 社交沟通功能受损的原因。

DSM-5 将 ASD 的诊断划分为一种谱系障碍，希望研究人员及临床医生采用更具维度的方法来研究 ASD 这种连续变化的谱系障碍，而不是将 ASD 划分为独立的亚型(Kim, 2020)。Tang 等人基于这一观点提出了一种全新的分析框架，将 ASD 的异常功能连接模式分解成了三种因子，不同的 ASD 被试对于这三种因子表达程度不同，且不同因子的表达程度与临床症状相关(Tang et al., 2020)。Tang 等人提出的分析框架对于揭示 ASD 的异质性向前迈进了一步，后续的研究还需要探索这种基于功能连接获得的 ASD 维度特征背后的分子机制及在实现 ASD 精准诊疗过程中的作用。

基于亚型及维度划分的 ASD 脑影像研究致力于探索 ASD 高度异质性的神经机制。然而，大多数研究都是基于单模态脑影像。如何融合多模态的磁共振脑影像，建立亚型/维度与 ASD 临床症状、神经干预疗效等这些临床指标之间的关系，探索适合不同亚型/维度的个体化诊疗策略是未来 ASD 研究的一个重要方向。

6 小结与展望

本文从 ASD 单模态脑影像研究、多模态脑影像融合研究、辅助诊断、亚型识别几个方面总结了现有的研究结果。回顾以往的研究发现，多模态磁共振脑影像研究丰富了我们对 ASD 神经病理机制的认识，为揭示 ASD 的神经机制提供了强有力的手段，有望推动孤独症临床诊疗从依据主观判断到客观指标的转变。然而，影像学的发现距离临床实现精准诊疗还具有很远的距离，未来的研究还需要继续着力关注以下几个问题：

6.1 融合多模态脑影像实现 ASD 全面表征

现阶段，ASD 的影像学研究大多是单模态、小样本研究，获得的结果往往具有一定的差异，且无法全面刻画 ASD 大脑结构与功能的细微变化。基于大样本、多中心的多模态脑影像融合技术为多尺度、多层级对 ASD 进行表征提供了新的手段。然而，无论是利用图像级融合、特征级融合还是决策级融合的 ASD 研究都处于起步阶段。未来的研究可以基于多模态脑影像融合技术，发展低维度、个体化、参数化的分析框架，全面揭示 ASD 的异常神经常制，寻找具有分类识别能力的影像学标记物，为实现 ASD 的辅助诊断及亚型分类提供客观依据。

再者，基于脑电的研究发现 ASD 的频谱功率、相干性以及半球不称性均存在异常(Wang et al., 2013)；基于眼动追踪的研究发现 ASD 相较于 TD 对面孔图片以及社会性图片都表现出了异常的注视模式(Kou et al., 2019; Wang et al., 2020)；肠道菌群的研究也发现 ASD 肠道菌群失调可能通过免疫反应、肠胃系统等通路来影响脑与行为之间的关系(McElhanon et al., 2014; Noriega & Savelkoul, 2014; Vuong & Hsiao, 2017)。脑电、眼动追踪、肠道菌群等多源数据也有望为揭示 ASD 病理机制提供支撑。在今后的研究中，除了多模态脑影像数据，还可以纳入电生理、眼动追踪数据、生化指标这些多源信息来构建多中心、大样本、多源异构数据库，有效利用各模态的数据优势，加强信息互补，多维度、全方位探索 ASD 发生发展规律。

6.2 揭示“社会脑”网络异常机制

回顾 ASD 脑影像的研究，发现大多数的异常区域都集中在了“社会脑”网络，“社会脑”网络是 ASD 大脑在不同层次上受影响最大的脑区。以往的结果在一定程度上支持了 ASD 的社交动机理论假说。“社会脑”网络主要包括的区域有内侧前额叶、腹内侧前额叶、后颞上沟、楔前叶、梭状回、额下回、额叶-脑岛皮质、杏仁核(L. Li et al., 2021; Misra, 2014; Sato & Uono, 2019)。这些脑区主要负责处理社会性刺激，例如，面孔识别、情感加工处理、眼睛注视、

心智理论等(Sato & Uono, 2019)，这恰好与 ASD 的社交沟通等高级认知功能损伤相符合，因此“社会脑”网络的异常可能导致大脑信息处理和整合障碍，进而影响 ASD 的社交、沟通以及行为表现。后续的研究可以融合多模态脑影像，着力揭示 ASD “社会脑” 网络的影像学机制。

在过去的十多年，经颅磁刺激作为一种非入侵性的神经调控技术，在临床研究中得到了广泛的应用，成为了对包括 ASD 在内的神经发育障碍及精神疾病治疗的新选择(Iglesias, 2020; Kang et al., 2019; Memon, 2021)。选择恰当的刺激靶点是取得预期调控效果的关键。例如，初级运动皮层被用来提升运动控制、进行康复训练以及治疗运动障碍；前额叶皮层被用来改善执行功能、工作记忆、决策能力以及情绪调节；颞叶区域被用来治疗言语障碍以及情绪障碍等。然而，现有神经调控研究中对于 ASD 社交核心症状的改善程度有限。基于现有的 ASD 脑影像研究结果，我们推荐将来研究可以将“社会脑”网络中的关键节点(例如，背外侧前额叶)作为刺激区域，以此来改善 ASD 的社交障碍。然而，未来还需要大量的临床实证来验证这一推论。

6.3 助力临床实现精准诊疗

早期精确诊断可以为 ASD 儿童提供更早的干预治疗，有助于制定个性化的教育和康复方案。然而，ASD 儿童异质性强，且传统诊断方式需要经验丰富的专业人员进行评估，这使得早期诊断变得更加复杂。多模态磁共振脑影像为 ASD 的辅助诊疗提供了新的手段，但是还面临着样本量小、模型参数维度高、可解释性差、泛化能力差、多模态数据融合难、多中心数据协调没有完善策略、早期预警难、异质性强等诸多问题。因此，将来的研究需要基于多中心、大样本数据深入挖掘具有早期诊断能力的影像学标记物，建立具有可推广性、稳定性的 ASD 早期预警及诊断模型，从而实现早诊断、早干预。在此基础上，建立基于多模态脑影像的疗效评估模型，针对 ASD 不亚型/维度制定不同干预策略，优化传统单一的治疗方案，为临床实现精准诊疗提供客观依据。

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Multimodal magnetic resonance imaging pattern recognition in autism spectrum disorder

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Abstract: Autism spectrum disorder (ASD) is a highly complex neurodevelopmental disorder characterized by high prevalence, heterogeneity, and lifelong impact. The underlying mechanisms of ASD remain largely unknown. Multimodal magnetic resonance imaging (MRI) has emerged as a novel tool to unveil the neuroimaging mechanisms of ASD. Studies based on single-modal MRI have already revealed widespread abnormalities in brain structure, function, and network connectivity in individuals with ASD. The affected regions encompass the amygdala, fusiform gyrus, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex, superior temporal sulcus, and insula, many of which are implicated in the "social brain" network. While frameworks for multimodal brain imaging analysis, involving image-level fusion, feature-level fusion, and decision-level fusion, offer multidimensional and multilevel information for understanding neural mechanisms in participants, research on ASD based on multimodal MRI fusion is still in its early stages. Moreover, ASD-assisted diagnosis and subtype classification models based on MRI features hold promise for providing objective evidence for clinical diagnosis and treatment. Future research should aim to construct an integrated analysis framework that fuses multimodal brain imaging, incorporating information from various dimensions such as brain function, structure, and networks. This approach will comprehensively delineate the developmental patterns of ASD and reveal its atypical neurodevelopmental mechanisms. Additionally, future studies need to delve into the abnormal mechanisms of the "social brain" network in ASD, explore social impairment circuits, and identify potential precision neural regulatory targets, thereby assisting clinical efforts in achieving precise diagnosis and treatment for ASD.

Keywords: ASD, multimodal magnetic resonance imaging, brain structure and function, ASD-assisted diagnosis, subtype classification